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Cell Size Regulation Induces Sustained Oscillations in the Population Growth Rate

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Cell size regulation induces sustained oscillations in the population growth rate

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We study the effect of correlations in generation times on the dynamics of population growth of microorganisms. We show that any non-zero correlation that is due to cell-size regulation, no matter how small, induces long-term oscillations in the population growth rate. The population only reaches its steady state when we include the often-neglected variability in the growth rates of individual cells. We discover that the relaxation time scale of the population to its steady state is determined by the distribution of single-cell growth rates and is surprisingly independent of details of the division process such as the noise in the timing of division and the mechanism of cell-size regulation. We validate the predictions of our model using existing experimental data and propose an experimental method to measure single-cell growth variability by observing how long it takes for the population to reach its steady state or balanced growth.

Most of us have first cousins that are more or less our age, but the ages of our more distant cousins are more broadly distributed. The difference arises due to the larger number of generations since our last common ancestor with our more distant cousins. The noise in the generation times adds up over generations, giving rise to wider distributions of ages. The number of generations it takes for the descendants of an individual to sufficiently mix in age to be statistically indistinguishable from the rest of the population is inversely related to the variability in the generation times [1].

Here, we show that this problem is very different in the context of single-cellular organisms due to the interaction between cell size and generation time. Many single-cellular organisms grow exponentially in size before division [2–9]. If a cell grows for a longer time than expected before it divides, its daughter cells will be larger at birth and have to compensate for their sizes by dividing slightly earlier than expected. Otherwise, the noise in the generation times would accumulate over generations in the size of the cells, leading to extremely large cells [10]. This compensation for the error in the generation times not only suppresses the accumulation of noise in cell sizes, but also prevents the accumulation of noise in the distribution of ages over generations and keeps the division times synchronized (see Fig. 1). Given this observation, it is natural to ask what sets the time scale for a population of microorganisms to desynchronize and reach its steady state.

In this Letter, we study the dynamics of population growth of microorganisms starting from a single cell. We show that the correlations induced by the cell-size control mechanism, no matter how small, significantly delay the relaxation of the population to its steady state. We observe transient oscillations in the growth rate of the number of cells in the population. These oscillations are sustained by the mother-daughter correlations and decay due to the competing effect of small variations in the single-cell growth rates. We discover that the single-cell growth rate distribution completely determines the timescale for the relaxation of the population to its steady state as well as the steady state population growth rate irrespective of the details of cell division process and cell-size control mechanism.

The distribution of single-cell growth rates is a major evolutionary trait contributing to the fitness of an organism [11–13]. It has been recently shown that the steady-state growth rate of a population can be found from the distribution of single-cell growth rates [14, 15]. Since the population growth rate is easier to measure than the single-cell growth rate distribution, it would be desirable to go in the reverse direction. We provide a relationship between the decay rate of the oscillations in the growth rate of the population and the distribution of single-cell growth rates. This relationship can be used in combination with steady-state results to estimate the growth rate distribution by observing the growth of a population as it relaxes to its steady state. We validate this prediction using the existing single cells data from the "mother machine" experiment from Ref. [2].

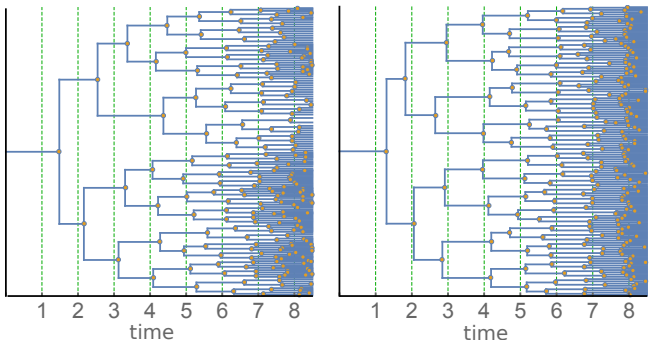

FIG. 1. Lineage tree of populations starting from a single cell. (left) In the absence of cell size control, the division times (circular markers) become less synchronized over time due to the accumulation of noise in their generation times. (right) The division times of cells with cell size control stay synchronized due to correlations in the generation times of mother and daughter cells.

We use a model introduced in Ref. [10], where cells grow exponentially in size with growth rate κ. Each cell with birth size v_b attempts to divide after its size reaches a target size $v_d = f(v_b)$. We assume a time additive[1] noise ξ in the division process with zero mean and variance σ_ξ^2 such that the generation time τ is given by

$$\tau = \frac{1}{\kappa} \ln\left(\frac{v_d}{v_b}\right) + \xi. \tag{1}$$

The function $f(v_b)$ determines the cell-size control mechanism. In the presence of cell-size control, the sequence of initial sizes, $v_b^{n+1} = f(v_b^n)/2$ has a fixed point Δ, and the distribution of initial cell sizes is sharply peaked around Δ. Therefore, all reasonable functions f that are equivalent to linear order near Δ describe approximately the same dynamics. The one parameter family of functions $f(v_b) = 2\Delta^\alpha v_b^{1-\alpha}$, with $0 \le \alpha \le 1$ qualitatively captures the full range of behavior for this model and interpolates between two extremes [10, 16]. The case $\alpha = 0$, known as the timer model, has no cell size control where cells attempt to divide after a period of time independent of their size. Successive generation times in this case are uncorrelated with variance σ_ξ^2 while the variance of the cell size distribution is known to diverge at long time [10]. The case $\alpha = 1$ is known as the sizer model where cells attempt to divide when they reach the size 2Δ independent of their history [17]. Experimental data support a value of α closer to $1/2$ for many organisms, where cells attempt to divide when they approximately add a constant size Δ to their original size [3, 6, 9, 10, 18–23]. For $\alpha > 0$, the generation times of mother and daughter cells are correlated with Pearson correlation coefficient $C_{MD} = -\alpha/2$ [14], and variance of the generation time is given by $2\sigma_\xi^2/(2-\alpha)$.

For a population starting from a single cell, the timing of the nth division, t_n, is given by

$$t_n = \sum_{i=1}^{n} \tau_i = n\bar{\tau} + \delta t_n, \tag{2}$$

where $\bar{\tau} = \ln(2)/\kappa$ is the cell-size doubling time and δt_ns are random variables with probability density $g_n(\delta t)$. We have derived the following recursive relationship for g_n (See the Supplemental Material (SM) [24] for the derivation)

$$g_n(\delta t) = \int g_{n-1}(\delta t - \delta\tau) f_\xi\big((1-\alpha)\delta\tau + \alpha\delta t\big) d\delta\tau, \tag{3}$$

where f_ξ is the probability density function of ξ. The expected value of the rate of change in the total number of cells in the population can be written as the sum of the division rates (number of cells produced in each generation multiplied by the division time distribution) over all generations

$$\frac{dN}{dt} = \sum_{n=1}^{\infty} 2^n g_n(t - n\bar{\tau}). \tag{4}$$

For $\alpha = 0$, the integral in Eq. (3) becomes a convolution leading to the accumulation of the noise at each generation. For $0 < \alpha \le 1$, the variance of the division time at the nth generation is found using Eq. (3) to be

$$\mathrm{var}(t_n) = \sigma_\xi^2 \frac{1-(1-\alpha)^{2n}}{\alpha(2-\alpha)}. \tag{5}$$

For $\alpha > 0$, the successive division time distributions approach a limiting distribution with the finite variance $\sigma_\xi^2/\alpha(2-\alpha)$. The negative correlations induced by cell-size control[2] prevent the cells from desynchronizing, and

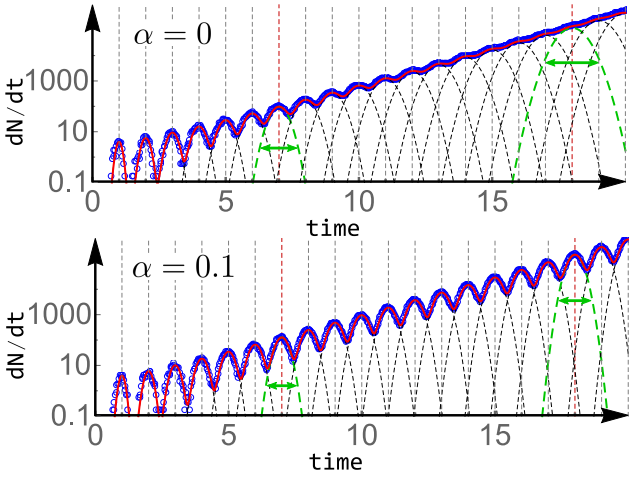

FIG. 2. Log-scale plot of the expected value of the rate of change of the number of cells in a population starting with a single cell, calculated analytically (red solid curve) and compared with simulation (blue circles). The rate of change of the number of cells can be written as the sum of the division rates (parabolic dashed lines) of all generations (see Eq. (3)). (Top) In the absence of cell size control, $\alpha = 0$, the distribution of division times of higher generations get wider and start to overlap, damping out the oscillations in the growth rate. (Bottom) In the presence of even a small cell size control, $\alpha = 0.1$, the distribution of successive division times quickly approach a steady state distribution with a finite variance (see Eq. (5)) leading to the persistence of oscillations in the growth of the population. The distribution of timing of the 7th and 18th generations are highlighted in both cases for comparison.

[1] Simulations results (not shown here) indicate that the dynamics is not affected if size-additive noise is used instead.

[2] Negative correlations between the generation times of mother and daughter cells that are not due to cell size control are not

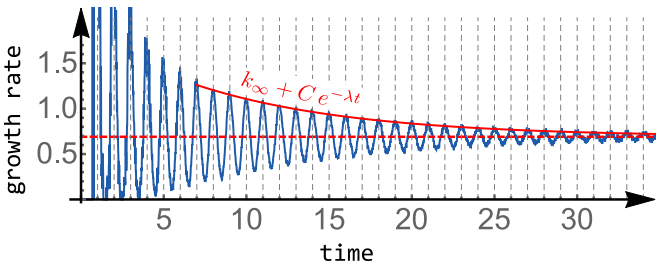

FIG. 3. Oscillations in the population growth rate decay exponentially due to the stochasticity in growth rates of individual cells. The solid red line is the exponential fit used in Fig. 4, the horizontal dashed red line is the steady-state value of the population growth rate, and vertical dashed lines are the expected values of successive division times where the population growth rate peaks. Simulation parameters: $\alpha = 0.5$, $\sigma_\xi = 0.1$, $\bar{\kappa} = \ln(2)$, and $\sigma_\kappa = 0.07\bar{\kappa}$.

the change in the population is characterized by periodic bursts of divisions at regular intervals. Here, we have made no assumption about the distribution of the noise ξ in the timing of the division process except that it has a finite variance. For a more concrete example, let us consider a Gaussian form for f_ξ[3]. In this case, using Eq. (3), we are able to show that the g_ns are also Gaussian distributed with the variance given in Eq. (5). Figure 2 shows the comparison of these analytical results with the numerical simulations for two cases of no cell size control, $\alpha = 0$, and a small cell size control, $\alpha = 0.1$.

In practice, a population of uncoupled cells cannot maintain synchronized division for infinite time and the oscillations in the growth rates have to decay as the population relaxes to its steady-state age distribution. In order to capture this relaxation and estimate its time scale, we need to include multiple sources of noise in our model. There are at least two other sources of stochasticity in the growth and division of cells: (1) small variability in the growth rate of the individual cells from one generation to another and (2) random asymmetry in the division plane of otherwise symmetrically dividing cells. In many symmetrically dividing organisms, the coefficient of variation (CV, the ratio of the standard deviation to the mean) of the single-cell growth rate, κ, is significantly larger than that of the division ratio (DR, the ratio of the size of the daughter cell to that of its mother cell). For example in *E. coli*, the CV of DR is between 0.02 and 0.06 [3, 9, 25] while the CV of single-cell growth rate is reported to be between 0.06 and 0.20 depending on the growth condition [14, 26–28]. Here we consider organisms in which the stochasticity in the DR can be neglected. The extension of our results with stochastic DR is studied in SM [24]. Since κ has a narrow symmetric distribution around its mean $\bar{\kappa}$ [28], its distribution can be estimated as a Gaussian with some variance σ_κ^2. Furthermore, unlike the correlation in the generation times, the correlation between the growth rate of mother and daughter cells can be negligible depending on the organism and the growth condition [2, 29] and are ignored in this model.

Figure 3 shows the population growth rate, $k \equiv d\ln(N)/dt$, in a simulation of the model described above, where now the growth rate of each cell is independently chosen from a Gaussian distribution with the mean $\bar{\kappa} = \ln(2)$ and CV of 0.07 (time is measured in the unit of $\bar{\tau} = \ln(2)/\bar{\kappa}$). We observe that oscillations in the population growth rate decay exponentially at long time until the growth rate approaches a steady state value. This value is given by the unique k satisfying the equation

$$\left\langle \left(\frac{1}{2}\right)^{k/\kappa} \right\rangle_\kappa \equiv \int_0^\infty \rho(\kappa)\, 2^{-k/\kappa} d\kappa = \frac{1}{2} \qquad (6)$$

where $\rho(\kappa)$ is the distribution of single-cell growth rates (see SM [24] for derivation). In Eq. (6), ρ is the distribution along a lineage (or equivalently over the entire population tree) which is distinct from the instantaneous population distribution [14, 30, 31]. Since the slow-growing cells have longer generation times, they are overrepresented in the population at any given time, and therefore, the population growth rate is slightly smaller than $\bar{\kappa}$ [4]. For a narrow distribution, the population growth rate can be approximated in terms of $\bar{\kappa}$ and σ_κ [15]

$$k \approx \bar{\kappa} - \left(1 - \frac{\ln(2)}{2}\right)\frac{\sigma_\kappa^2}{\bar{\kappa}}. \qquad (7)$$

We have a total of five independent variables in our model: α, σ_ξ, σ_κ, Δ, and $\bar{\tau} = \ln(2)/\bar{\kappa}$. Time and size can be measured in units of $\bar{\tau}$ and Δ, respectively. Figure 4 shows the dependence of the rate of decay of the oscillations of the population growth rate on all of the remaining model parameters α, σ_ξ, and σ_κ. Surprisingly, this decay rate is completely independent of the mechanism of cell size control, α (with the exception of the single point $\alpha = 0$), and is also independent of the noise in the timing of the division process, σ_ξ. It is proportional to the variance of the single-cell growth rate, σ_κ^2.

sufficient to sustain these oscillations. This can be shown by a model in which $\tau_{i+1} = \bar{\tau} - \alpha(\tau_i - \bar{\tau}) + \xi_i$ independent of the size of the cell. In this model, for all values of $\alpha > 0$, the accumulation of the noise is only partially suppressed and the oscillations decay at long time.

[3] We assume the variance is small enough so that τ does not become negative.

[4] This argument fails if the growth rates of mother and daughter cells are highly correlated, in which case the fast-growing cells reproduce faster and can potentially compensate for their underrepresentation in the population depending on the strength of the correlation. See Ref. [15] for a more detailed discussion.

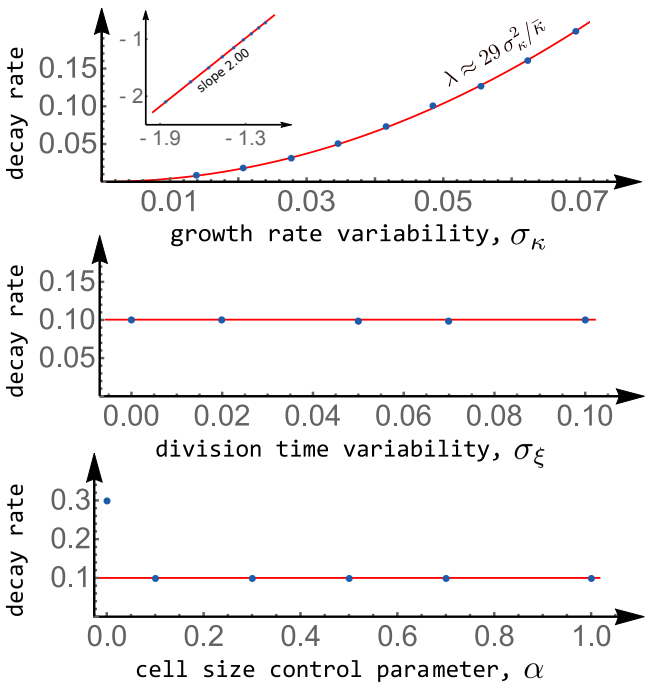

FIG. 4. Simulation results for the decay rate of oscillations in the population growth rate shown as functions of σ_κ, σ_ξ, and α: (top) decay rate increases linearly with the variance of single-cell growth rate distribution, σ_κ^2 (the red solid line is a parabolic fit; inset is the log-log plot with linear fit); (middle) the noise in the division process has no effect on the damping of the oscillations in the population growth rate; (bottom) the mechanism for cell-size control does not affect the decay rate either as long as there is a nonzero cell-size control, $\alpha \neq 0$. Simulation parameters: (top) $\alpha = 0.5$ and $\sigma_\xi = 0.1\bar{\tau}$, (middle) $\alpha = 0.5$ and $\sigma_\kappa = 0.07\bar{\kappa}$, and (bottom) $\sigma_\xi = 0.1\bar{\tau}$ and $\sigma_\kappa = 0.07\bar{\kappa}$.

As seen in Fig. 3, for a realistic value of single-cell growth rate variability, the oscillations in the population growth rate can be observed for as long as 40 generations. A test tube culture of *E. coli* starting from a single cell begins to saturate after about 30 generations ($\sim 10^9$ cells/ml) making these oscillations visible at any time during the exponential growth phase[5]. This allows the measurement of both the steady state population growth rate k and the decay rate λ. From Fig. 4, the decay rate λ is approximately given by $\lambda \approx 29\,\sigma_\kappa^2/\bar{\kappa}$ which combined with Eq. (7) provides both the mean and the variance of single-cell growth rates, $\bar{\kappa}$ and σ_κ^2. This method for measuring the variability in single-cell growth rates is significantly easier and less biased than the direct single cell measurement.

[5] These oscillations are hidden to the optical density measurements which provide a proxy for the total mass of the population. Cell counting techniques should be used instead to detect these oscillations.

To validate this method, we use existing single-cell data from the "mother machine" experiment from Ref. [2]. Unlike the proposed experiment where all the cells share a common ancestor at time zero, this experiment provides an ensemble of unrelated single cell lineages. However, there is a proper shift of the time frame for each lineage after which at long time, the division times of all lineages become synchronized as though they were descendants of the same cell (see SM [24] for details). Figure 5 shows the exponential decay of the oscillation in the histogram of the division times across all lineages after proper synchronization. The inferred single cell growth rate variability σ_κ shows excellent agreement with the direct measurement of this quantity.

Conclusion : For nearly a century, microbiologists have been concerned with the relationship between statistical observables of single cells and the properties of their populations [22, 32–37]. Recent advances in single-cell tracking technology has lead to a surge of renewed interest in this field [2, 38–43]. On one hand, the details of the mechanism of cell size control that allows populations to maintain a narrow distribution of cell sizes [35, 44–51] has become the topic of an intense debate over the past few years [3, 6, 10, 16, 27, 52–56]. On the other hand, the relationship between the stochasticity in the generation times of microorganisms and the growth of their populations has gained recent attention [1, 28, 30, 31, 57–59]. There are two distinct sources of stochasticity in generation times: the noise in the cellular growth and the noise in the division process. We claim that only the former plays a role in the growth and relaxation rates of the population, while cell size control is precisely the process of canceling out the latter over the course of a few generations. As a result, both the time it takes for a population to reach its steady state and the steady-state population growth rate are only affected by the portion of noise in the generation times that is due to the variability in the single-cell growth rates and not the stochasticity in the

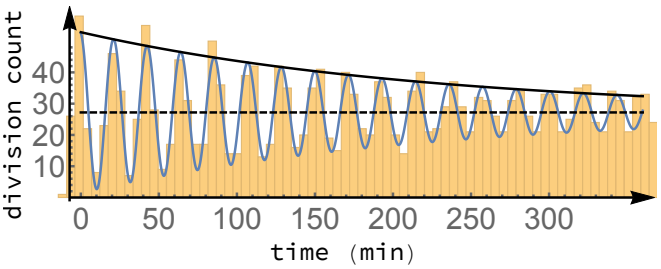

FIG. 5. Histogram of division times in a synchronized ensemble of single cell lineages from Ref. [2] (see SM [24] for details). The decay rate of these oscillations is measure to be $\lambda \approx (0.27 \pm 0.03)\ hour^{-1}$ which determines the variability in single-cell growth rates of $\sigma_\kappa = (0.130 \pm 0.007)\ hour^{-1}$ compared to direct measurement of the sample standard deviation $\sigma_\kappa = 0.135\ hour^{-1}$.

timing of cell division. A practical consequence of this result is that the distribution of single-cell growth rates can be estimated by observing how long it takes for a population starting from a single cell to reach its steady state. Analysis of single cells data from the "mother machine" experiment shows excellent quantitative agreement with this prediction.

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[1] Farshid Jafarpour, Charles S Wright, Herman Gudjonson, Jedidiah Riebling, Emma Dawson, Klevin Lo, Aretha Fiebig, Sean Crosson, Aaron R Dinner, and Srividya Iyer-Biswas, "Bridging the timescales of single-cell and population dynamics," Physical Review X **8**, 021007 (2018).

[2] Ping Wang, Lydia Robert, James Pelletier, Wei Lien Dang, Francois Taddei, Andrew Wright, and Suckjoon Jun, "Robust growth of escherichia coli," Current biology **20**, 1099–1103 (2010).

[3] Manuel Campos, Ivan V Surovtsev, Setsu Kato, Ahmad Paintdakhi, Bruno Beltran, Sarah E Ebmeier, and Christine Jacobs-Wagner, "A constant size extension drives bacterial cell size homeostasis," Cell **159**, 1433–1446 (2014).

[4] Srividya Iyer-Biswas, Charles S Wright, Jonathan T Henry, Klevin Lo, Stanislav Burov, Yihan Lin, Gavin E Crooks, Sean Crosson, Aaron R Dinner, and Norbert F Scherer, "Scaling laws governing stochastic growth and division of single bacterial cells," Proceedings of the National Academy of Sciences **111**, 15912–15917 (2014).

[5] Srividya Iyer-Biswas, Gavin E Crooks, Norbert F Scherer, and Aaron R Dinner, "Universality in stochastic exponential growth," Physical review letters **113**, 028101 (2014).

[6] Sattar Taheri-Araghi, Serena Bradde, John T Sauls, Norbert S Hill, Petra Anne Levin, Johan Paulsson, Massimo Vergassola, and Suckjoon Jun, "Cell-size control and homeostasis in bacteria," Current Biology **25**, 385–391 (2015).

[7] Dan Pirjol, Farshid Jafarpour, and Srividya Iyer-Biswas, "Phenomenology of stochastic exponential growth," Physical Review E **95**, 062406 (2017).

[8] Stefano Di Talia, Jan M Skotheim, James M Bean, Eric D Siggia, and Frederick R Cross, "The effects of molecular noise and size control on variability in the budding yeast cell cycle," Nature **448**, 947 (2007).

[9] Ye-Jin Eun, Po-Yi Ho, Minjeong Kim, Salvatore LaRussa, Lydia Robert, Lars D Renner, Amy Schmid, Ethan Garner, and Ariel Amir, "Archaeal cells share common size control with bacteria despite noisier growth and division," Nature microbiology **3**, 148 (2018).

[10] Ariel Amir, "Cell size regulation in bacteria," Physical Review Letters **112**, 208102 (2014).

[11] Daniele De Martino, Fabrizio Capuani, and Andrea De Martino, "Growth against entropy in bacterial metabolism: the phenotypic trade-off behind empirical growth rate distributions in e. coli," Physical biology **13**, 036005 (2016).

[12] Takashi Nozoe, Edo Kussell, and Yuichi Wakamoto, "Inferring fitness landscapes and selection on phenotypic states from single-cell genealogical data," PLoS genetics **13**, e1006653 (2017).

[13] Lydia Robert, Jean Ollion, Jerome Robert, Xiaohu Song, Ivan Matic, and Marina Elez, "Mutation dynamics and fitness effects followed in single cells," Science **359**, 1283–1286 (2018).

[14] Jie Lin and Ariel Amir, "The effects of stochasticity at the single-cell level and cell size control on the population growth," Cell systems **5**, 358–367 (2017).

[15] Jie Lin and Ariel Amir, "Population growth with correlated generation times at the single-cell level," arXiv preprint arXiv:1806.02818 (2018).

[16] Po-Yi Ho, Jie Lin, and Ariel Amir, "Modeling cell size regulation: From single-cell-level statistics to molecular mechanisms and population-level effects," Annual review of biophysics **47**, 251–271 (2018).

[17] Odo Diekmann, HA Lauwerier, T Aldenberg, and JAJ Metz, "Growth, fission and the stable size distribution," Journal of mathematical biology **18**, 135–148 (1983).

[18] Suckjoon Jun and Sattar Taheri-Araghi, "Cell-size maintenance: universal strategy revealed," Trends in microbiology **23**, 4–6 (2015).

[19] John T Sauls, Dongyang Li, and Suckjoon Jun, "Adder and a coarse-grained approach to cell size homeostasis in bacteria," Current opinion in cell biology **38**, 38–44 (2016).

[20] Michelle M Logsdon, Po-Yi Ho, Kadamba Papavinasasundaram, Kirill Richardson, Murat Cokol, Christopher M Sassetti, Ariel Amir, and Bree B Aldridge, "A parallel adder coordinates mycobacterial cell-cycle progression and cell-size homeostasis in the context of asymmetric growth and organization," Current Biology **27**, 3367–3374 (2017).

[21] Shiladitya Banerjee, Klevin Lo, Matthew K Daddysman, Alan Selewa, Thomas Kuntz, Aaron R Dinner, and Norbert F Scherer, "Biphasic growth dynamics control cell division in caulobacter crescentus," Nature microbiology **2**, 17116 (2017).

[22] Suckjoon Jun, Fangwei Si, Rami Pugatch, and Matthew Scott, "Fundamental principles in bacterial physiology-history, recent progress, and the future with focus on cell size control: a review," Reports on Progress in Physics **81**, 056601 (2018).

[23] Fangwei Si, Guillaume Le Treut, John T Sauls, Stephen Vadia, Petra Anne Levin, and Suckjoon Jun, "Mechanistic origin of cell-size control and homeostasis in bacteria," bioRxiv , 478818 (2018).

[24] See Supplemental Material at [URL] for the experimental validation of the model with existing data, the derivation of Eq. (3), analysis of the model with stochastic division ratio, and the analysis of steady state population growth rate.

[25] Jonathan M Guberman, Allison Fay, Jonathan Dworkin, Ned S Wingreen, and Zemer Gitai, "Psicic: noise and asymmetry in bacterial division revealed by computational image analysis at sub-pixel resolution," PLoS com-

putational biology **4**, e1000233 (2008).
[26] Nathan Cermak, Selim Olcum, Francisco Feijó Delgado, Steven C Wasserman, Kristofor R Payer, Mark A Murakami, Scott M Knudsen, Robert J Kimmerling, Mark M Stevens, Yuki Kikuchi, *et al.*, "High-throughput measurement of single-cell growth rates using serial microfluidic mass sensor arrays," Nature biotechnology **34**, 1052 (2016).
[27] Mats Wallden, David Fange, Ebba Gregorsson Lundius, Özden Baltekin, and Johan Elf, "The synchronization of replication and division cycles in individual e. coli cells," Cell **166**, 729–739 (2016).
[28] Andrew S Kennard, Matteo Osella, Avelino Javer, Jacopo Grilli, Philippe Nghe, Sander J Tans, Pietro Cicuta, and Marco Cosentino Lagomarsino, "Individuality and universality in the growth-division laws of single e. coli cells," Physical Review E **93**, 012408 (2016).
[29] Jacopo Grilli, Clotilde Cadart, Gabriele Micali, Matteo Osella, and Marco Cosentino Lagomarsino, "The empirical fluctuation pattern of e. coli division control," Frontiers in microbiology **9** (2018).
[30] Nash D Rochman, Dan M Popescu, and Sean X Sun, "Ergodicity, hidden bias and the growth rate gain," Physical biology **15**, 036006 (2018).
[31] Lee Susman, Maryam Kohram, Harsh Vashistha, Jeffrey T Nechleba, Hanna Salman, and Naama Brenner, "Individuality and slow dynamics in bacterial growth homeostasis," Proceedings of the National Academy of Sciences , 201615526 (2018).
[32] AG M'Kendrick, "Applications of mathematics to medical problems," Proceedings of the Edinburgh Mathematical Society **44**, 98–130 (1925).
[33] EO Powell, "Growth rate and generation time of bacteria, with special reference to continuous culture," Microbiology **15**, 492–511 (1956).
[34] H Von Foerster and F Stohlman, "The kinetics of cellular proliferation," Grune & Stratton **3** (1959).
[35] PR Painter and AG Marr, "Mathematics of microbial populations," Annual Reviews in Microbiology **22**, 519–548 (1968).
[36] Benoît Perthame, *Transport equations in biology* (Springer Science & Business Media, 2006).
[37] Andrew Rubin and Galina Riznichenko, *Mathematical biophysics* (Springer, 2016).
[38] Yuichi Wakamoto, Jeremy Ramsden, and Kenji Yasuda, "Single-cell growth and division dynamics showing epigenetic correlations," Analyst **130**, 311–317 (2005).
[39] Dan Siegal-Gaskins and Sean Crosson, "Tightly regulated and heritable division control in single bacterial cells," Biophysical Journal **95**, 2063–2072 (2008).
[40] Oleksii Sliusarenko, Jennifer Heinritz, Thierry Emonet, and Christine Jacobs-Wagner, "High-throughput, subpixel precision analysis of bacterial morphogenesis and intracellular spatio-temporal dynamics," Molecular microbiology **80**, 612–627 (2011).
[41] Jonathan W Young, James CW Locke, Alphan Altinok, Nitzan Rosenfeld, Tigran Bacarian, Peter S Swain, Eric Mjolsness, and Michael B Elowitz, "Measuring single-cell gene expression dynamics in bacteria using fluorescence time-lapse microscopy," Nature protocols **7**, 80 (2012).
[42] Hanna Salman, Naama Brenner, Chih-kuan Tung, Noa Elyahu, Elad Stolovicki, Lindsay Moore, Albert Libchaber, and Erez Braun, "Universal protein fluctuations in populations of microorganisms," Physical review letters **108**, 238105 (2012).
[43] Guillaume Lambert and Edo Kussell, "Quantifying selective pressures driving bacterial evolution using lineage analysis," Physical review X **5**, 011016 (2015).
[44] M Schaechter, Joan P Williamson, JR Hood Jun, and Arthur L Koch, "Growth, cell and nuclear divisions in some bacteria," Microbiology **29**, 421–434 (1962).
[45] AL Koch and M Schaechter, "A model for statistics of the cell division process," Microbiology **29**, 435–454 (1962).
[46] EC Anderson, GI Bell, DF Petersen, and RA Tobey, "Cell growth and division: Iv. determination of volume growth rate and division probability," Biophysical journal **9**, 246 (1969).
[47] Peter A Fantes, WD Grant, RH Pritchard, PE Sudbery, and AE Wheals, "The regulation of cell size and the control of mitosis," Journal of theoretical biology **50**, 213–244 (1975).
[48] Paul Jorgensen and Mike Tyers, "How cells coordinate growth and division," Current Biology **14**, R1014–R1027 (2004).
[49] An-Chun Chien, Norbert S Hill, and Petra Anne Levin, "Cell size control in bacteria," Current biology **22**, R340–R349 (2012).
[50] Jonathan J Turner, Jennifer C Ewald, and Jan M Skotheim, "Cell size control in yeast," Current biology **22**, R350–R359 (2012).
[51] Alison C Lloyd, "The regulation of cell size," Cell **154**, 1194–1205 (2013).
[52] Matteo Osella, Eileen Nugent, and Marco Cosentino Lagomarsino, "Concerted control of escherichia coli cell division," Proceedings of the National Academy of Sciences , 201313715 (2014).
[53] Lydia Robert, Marc Hoffmann, Nathalie Krell, Stéphane Aymerich, Jérôme Robert, and Marie Doumic, "Division in escherichia coli is triggered by a size-sensing rather than a timing mechanism," BMC biology **12**, 17 (2014).
[54] Andrew Marantan and Ariel Amir, "Stochastic modeling of cell growth with symmetric or asymmetric division," Physical Review E **94**, 012405 (2016).
[55] Jacopo Grilli, Matteo Osella, Andrew S Kennard, and Marco Cosentino Lagomarsino, "Relevant parameters in models of cell division control," Physical Review E **95**, 032411 (2017).
[56] Clotilde Cadart, Sylvain Monnier, Jacopo Grilli, Pablo J Sáez, Nishit Srivastava, Rafaele Attia, Emmanuel Terriac, Buzz Baum, Marco Cosentino-Lagomarsino, and Matthieu Piel, "Size control in mammalian cells involves modulation of both growth rate and cell cycle duration," Nature communications **9**, 3275 (2018).
[57] Mikihiro Hashimoto, Takashi Nozoe, Hidenori Nakaoka, Reiko Okura, Sayo Akiyoshi, Kunihiko Kaneko, Edo Kussell, and Yuichi Wakamoto, "Noise-driven growth rate gain in clonal cellular populations," Proceedings of the National Academy of Sciences **113**, 3251–3256 (2016).
[58] Bram Cerulus, Aaron M New, Ksenia Pougach, and Kevin J Verstrepen, "Noise and epigenetic inheritance of single-cell division times influence population fitness," Current Biology **26**, 1138–1147 (2016).
[59] Enrico Gavagnin, Matthew J Ford, Richard L Mort, Tim Rogers, and Christian A Yates, "The invasion speed of cell migration models with realistic cell cycle time distributions," arXiv preprint arXiv:1806.03140 (2018).